IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:

Jerry B. Gin, et al. Examiner: Lezah ROBERTS

Serial No.: 10/772,781 Group Art Unit: 1612

Filing Date: February 4, 2004 Confirmation No: 2376

Title: LONG-LASTING, FLAVORED DOSAGE FORMS FOR SUSTAINED RELEASE OF BENEFICIAL AGENTS WITHI THE MOUTH

SECOND DECLARATION OF JERRY B. GIN UNDER 37 C.F.R. §1.132

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I, Jerry B. Gin, Ph.D. hereby declare that:

1. I am a joint inventor of the subject matter claimed in the above-referenced United States patent application ("the '781 application").

2. I have been in the health care, pharmaceutical, and biotech fields for over 35 years. 1 received a Bachelor of Science in Chemistry from the University of Arizona and a Ph.D. in Biochemistry from the University of California, Berkeley. Early in my career, I directed the international pharmaceutical and diagnostic businesses for Dow Chemical. Thereafter, I was a Director of New Business Development and Strategic Planning for Syva, the diagnostic arm of Syntex Phannaceuticals. I then co-founded ChemTrak, the developer of the widely available home cholesterol test. In 1993, I co-founded my first drug delivery company, Oculex, which became one of the leading ophthalmic drug delivery companies. As President and CEO of Oculex, I developed the technology for controlled release of drugs to the interior of the eye, specifically to treat macular edema. I was formerly Chairman of Chakshu Research, a drug delivery company and currently serve as Chairman of Livionex, Inc., also a drug delivery company, and co-founded Nuvora, Inc., the assignee of the present patent application, in 2002. I have conducted research at the National Institutes of Health and am certified by the American Association for Clinical Chemistry and the American Society of Clinical Pathologists. I have contributed to numerous publications in clinical

chemistry and biochemistry, and am an inventor on more than 35 patents and applications, primarily in the areas of chemical formulation and drug delivery.

3. I reviewed the subject patent application and the pending claims, the Office Actions of record, including the final Office Action mailed July 18, 2011, and the references cited by the Examiner in the Office Action, namely, U.S. Patent No. 4,572,832 to Kigasawa; Lin *et al.* (J. Controlled Release 2001) and Tisserand (The Art of Aromatherapy, 1977). I also have reviewed references cited in previous Office Actions, namely U.S. Patent No. 4,528,125 to Alderman et al. ("Alderman"); US Pat. App. Pub. No. 2002/0054917 ("Gohlke"); and U.S. Patent No. 6,183,775 to Ventouras ("Ventouras").

4. After spending the past 20 years in working on sustained delivery systems, having general knowledge of the field and specifically looking at other patented technology related to essential oils and ethyl cellulose, I find that the sustained delivery system that is the subject matter of the pending claims in the instant patent application is unique and different from those disclosed in the cited references.

5. I previously provided a declaration dated August 27, 2009 where I distinguished the features of the claimed lozenges from those of Alderman and Ventouras, as well as described the commercial success of our solution to a long-felt need in the art.

6. I have been asked to provide this declaration in order to assist the Examiner in understanding the fundamental distinctions between the subject matter of the pending claims in the '781 patent application and the disclosure of the cited references.

7. As specified in the instant claims, as amended, the claimed composition is a non-swellable dosage form comprising a sustained release matrix formed by admixing micronized ethylcellulose with a flavoring agent selected from essential oils, constituents of essential oils, and mixtures thereof, "wherein the sustained release matrix is formed by a process consisting essentially of admixing the micronized ethylcellulose and the essential oil flavoring agent at room temperature and ambient humidity." No other steps are essential for the formation of the sustained-release matrix that comprises the dosage form.

8. The lozenge of the claimed invention is formed by simply admixing the two ingredients without any special treatments, such as granulation, for making the sustained release

matrix—as the interaction of the essential oil with ethyl cellulose creates a dough-like mass. Once the matrix sets, the claimed lozenges can be cut therefrom as disclosed in the '781 application.

9. The terpene structure of essential oils and its solvent effect on ethyl cellulose allows formation of the dough-like substance. This is described as the "soft, wet composition" in various examples in the '781 application. (*See*, Example 1, *et seq.*). Other oils (olive, coconut, palm, etc.), without the terpene structure, are unable to form the dough with ethyl cellulose. The ability to form a dough-like matrix that has sustained release properties is novel and unique and was not previously described in the literature. The claimed invention is applicable to all essential oils, but not to other oils that do not have a terpene structure.

10. The resulting lozenge according to the claimed invention is soft (like a moist cookie) and gradually erodes in the mouth to release the ingredients. The formation of the lozenge is dependent only on the presence of ethyl cellulose and the essential oils. While other ingredients may be added for a variety of other reasons, they are not the basis of forming the dough (sustained-release matrix) and the resulting dosage form. For example, in one embodiment of a lozenge for dry mouth, xanthan gum is added primarily to give the slippery feel of saliva.

11. This process of forming the claimed product is neither taught nor suggested by standard tablet making procedures which would not be workable in this context, as (a) there is no free-flowing powder to fill a tablet die, (b) the dough is tacky and would smear during ejection and (c) the high pressure compression required to form a tablet would not give the desired characteristics even if the tablet could be formed. Likewise, there is no encapsulation with ethyl cellulose since the process does not dissolve the ethyl cellulose for encapsulation purposes.

12. In contrast to the disclosure of the '781 application, artisans in the field of using ethyl cellulose and essential oils either make tablets with the ingredients or make a film to encapsulate, which often uses an additional solvent. Typically, the essential oil is most often used as a flavorant. In these cases, the tablet is formed based on the high compression of the ingredients, with appropriate binders to make the tablet and, for sustained release, appropriate materials to enhance release of the active ingredients. Often, the resulting lozenges are swellable. This is illustrated in the disclosures of every reference cited during the prosecution of this application, as discussed below.

13. The Kigasawa patent (US 4,572,832) teaches formation of a soft buccal that is distinctly different from the lozenge produced by the instant claims. Its formation is not based on

use of essential oils, other than its use as a possible flavorant. Its softness is based on use of a water soluble protein, fatty acid ester and/or a carboxyvinlyl polymer. The lozenge disclosed in the '781 application does not contain any water soluble protein or fatty acid or carboxyvinyl polymer. The basis of the Kigasawa patent is putting together soft wax-like materials to create the consistency of softness and a gelatin-like protein to hold everything together. The polyhydric alcohol is not for the purpose of holding the soft buccal together; this is typically accomplished by the use of an aqueous gelatin (the protein) that is heated and allowed to cool (the "jello" concept). In contrast, the lozenge disclosed in the '781 application is not a soft jello/wax-like structure; ethyl cellulose is a hard polymer that is held together with essential oils and its softness is based on the amount of essential oil used and the ethyl cellulose polymer and the essential oil are admixed to form the lozenge. The process does not use heat and water to dissolve a protein to allow cohesion of the ingredients. Thus, the process to form the lozenge disclosed in the '781 application is distinctly different than that used by Kigasawa whose lozenge bears no resemblance to it.

14. Lin *et al.* (J. Controlled Release 2001) discloses a coated tablet. The flavored non-swellable dosage form of the claimed invention is formed by a process that does not result in a tablet and there is no coating with ethyl cellulose. Lin teaches that micronization to fine particles presents a barrier for entry of water/solvent into the interior of the tablet containing the drug so that release rates can be modulated by surface particle size of the coating.(*See* Lin, Abstract). In the dosage forms of the claimed invention, the ethyl cellulose is uniform throughout the lozenge and ethyl cellulose on the surface is not used to affect release rates. The process Lin *et al* uses requires forming a core tablet with the active drug and then an outer dry coating of ethyl cellulose, resulting in a core and a coating. No such lozenge can be formed by the process disclosed in the '781 application since there is no "core," with all ingredients equally mixed throughout the lozenge matrix. For the Lin *et al* reference, the coating is the basis of the release characteristics, In contrast, for the claimed product lozenge prepared as disclosed in the '781 application, release of ingredients is not dependent on a coating and release is uniform throughout the lozenge because of the uniform composition.

15. The Ventouras patent (US 6,183,755) discloses lozenges that are distinctly different from that claimed in the instant invention application. The lozenges formed by the Ventouras patent procedure requires high compression due to the nature and high amounts of powders present and is thus a tablet forming process (see Ventouras at col. 5 line15 – col. 6 line 24). The patent teaches use

of a high amount of soluble filler (50 – 99%) and use of a swellable polymer (0.5 to 30%); neither filler nor swellable polymer are requirements for preparing lozenges according to the pending claims. The Ventouras patent does not teach forming a soft, pliable, non-tacky, dough-like substance that forms the lozenge.

16. The Gohlke application's (US 2002/0054917) lozenges require high pressure to form a tablet. Due to the nature of ingredients used, the lozenges are not "rock hard" so one can bite into them ("chew") and have a short residence time in the mouth, if chewed. In contrast, high pressure compression is not used in the process specified for formation of the dosage form of the claimed invention. Further, the Gohlke lozenges are not made with essential oil plus ethyl cellulose as the basis for its formation.

17. Kulkarni et al discloses consumable films made with water soluble polymers. The dosage form of the claimed Bennes invention is not based on the formation of rapidly dissolving films and uses a water insoluble polymer It is exactly opposite to that of dissolvable films in that the claimed dosage form is made by a process that results in a lozenge that will last sufficiently long in the mouth to be sure the ingredient can have enough time to have an effect. The lozenge disclosed in the '781 application "erodes" in the mouth and does not dissolve. In contrast, a consumable film will result in ingredients being dissolved and ending up primarily in the stomach rather than being able to work on the oral environment.

18. The claimed is product manufactured by the process disclosed in the '781 application is distinctly different from those described anywhere in the art cited during prosecution of the '781 application. (*See* Kigasawa, Ventouras, Lin, Gohlke, and Kulkarni discussed above). The method of manufacture disclosed in the '781 application does not have an "intermediate" that is formed in the process since once the ingredients are mixed together forming a soft, wet composition, and the product is formed once the mixture sets. Kigasawa, Ventouras, Lin, Gohlke, and Kulkarni do not disclose similar composition being formed even as "intermediates" during their process of manufacture. Kigasawa mixes waxy materials and gelatin; Ventouras mixes *swellable polymers* and fillers as a requirement before high pressure compression; Lin teaches *coating* a core tablet with ethyl cellulose; Gohlke makes chewable tablets to deliver colostrum/lactoferrin *without* the use of ethyl cellulose and does not require essential oils as flavorants; and Kulkarni mixes *water-soluble* polymers (not ethyl cellulose—which is not water soluble) with ingredients to form rapid dissolving films.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on belief and information are believed to be true; and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code, and that false statements may jeopardize the validity of this application or any patent issuing thereon.

Respectfully submitted

Date: Nov 18, 2011

By: Jerry B Gin

Declarant: Jerry B. Gin, Ph.D.